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Laterality Explored:
Atypical Hemispheric Dominance in Down Syndrome

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1. Introduction

Down syndrome (DS) is a genetic disorder caused by an extra copy of chromosome 21 (trisomy 21), with an incidence in 1 in 700 live births. The third chromosome causes a series of physical, biological and behavioural characteristics that are syndrome-specific including intellectual disability, heart defects, problems in the endocrine and immune system and other medical conditions (Epstein et al., 1991). Moreover, there is established evidence for the language difficulties in people with DS particularly in expressive vocabulary and grammar. Research on language has documented a specific pattern of cerebral lateralization that commonly characterizes these individuals, that is unique to the syndrome compared to typically developing individuals and individuals with intellectual disability (ID) non-DS. This realization has triggered the interest of neuropsychologists to investigate atypical hemispheric dominance in DS.

Atypical hemispheric Dominance, or otherwise termed "anomalous dominance" or "anomalous cerebral organization", refers to the atypical lateralization of language areas within the brain (Geschwind & Galaburda, 1985). Usually, most right-handed individuals (97%) exhibit left-hemisphere lateralization for language. The remaining 3% of right-handed individuals exhibit bilateral or right hemisphere lateralization for language (Bishop, 1990). In left-handed individuals this distribution is very different. About 60% of left-handed individuals exhibit left-hemisphere lateralization for language, 30% bilateral lateralization and 10% right-hemisphere lateralization for language (Bishop, 1990). Geschwind and Behan (1982) termed anomalous dominance that in which the pattern of language laterality differed from the "… standard dominance pattern" (pp. 70). Bryden, McManus and Bulman-Fleming (1994) criticized this definition, highlighting that if one accepts this description "… we run the risk of defining the majority of the population as being anomalous" (pp. 111). According to Gesch-

wind and Galaburda (1985a; 1985b), atypical dominance may involve the inverse or weak dominance of three features; hand dominance, language dominance and visuospatial dominance. Previc (1994) distinguished the term atypical laterality into anatomical atypical asymmetry, which involves the decreased volume of the left hemisphere compared to the right hemisphere, particularly in the temporal region, and is observed in approximately 30-35% of the normal population, and functional atypical asymmetry, which relates to the bilateral or right hemisphere language dominance.

During the past decades atypical laterality has been studied in a number of pathological conditions, including individuals with intellectual disability (ID) (e.g., Grouios, Sakadami, Poderi, & Alevriadou, 1999), DS (e.g., Heath & Elliott, 1999), autism (Cornish & McManus, 1996), Turner syndrome (Ganou & Grouios, 2008), Klinefelter syndrome (Ganou, Grouios, koidou, & Alevriadou, 2010), Williams syndrome (Järvinen-Pasley, Pollak, Yam, Hill, Grichanik et al., 2010), fragile-X syndrome (Cornish, Pigram, & Shaw, 1997), developmental stuttering (Foundas, Corey, Angeles, Bollich, Crabtree-Hartman et al., 2003), developmental dyslexia (Illingworth & Bishop, 2009), disabled reading (Dalby & Gibson, 1981), attention-deficit/hyperactivity disorder (Hale, Zaidel, McGough, Phillips, & McCracken, 2006), depression (Pinea, Kentgena, Bruderb, Leiteb, Bearmana et al., 2000), schizophrenia (Giotakos, 1999) and epilepsy (Slezicki, Cho, Brock, Pfeiffer, McVearry et al., 2009). The aim of the present review is to present and discuss research on atypical cerebral laterality in DS.

2. Laterality measures

There are several techniques with which one can assess the laterality of cognitive functions. A broad division of these techniques is that between invasive and non-invasive laterality measures.

An invasive technique is one, which penetrates or breaks the skin or enters a body cavity. The only available invasive technique for the assessment of lateralization of cognitive functions is the intracarotid amobarbital procedure (IAP) or Wada test. The IAP is a procedure first described by Wada (1949) and Wada and Rasmussen (1960) for anaesthetizing cerebral hemispheres for the purpose of lateralizing language and memory functions. The procedure consists of unilateral injection of sodium amobarbital into the internal carotid, which temporarily anaesthetizes the hemisphere ipsilateral to the injection site. While one hemisphere is anaesthetized, language and memory functions of the hemisphere contralateral to the injection site can be tested. After the effect of the anaesthesia has dissipated, the process is repeated with the other hemisphere. Determining the lateralization of language and memory functions is of both theoretical and practical interest, establishing cerebral language lateralization, predicting patients who are at risk for developing a post-surgical amnestic syndrome and identifying lateralized dysfunction to help confirm seizure onset laterality (Loring & Meador, 2000). Scientific investigation of cerebral lateralization in individuals with ID using the IAP is generally hampered for obvious moral and ethical reasons.

A scientific procedure is strictly defined as non-invasive when no break in the skin is created and there is no contact with the mucosa, or skin break, or internal body cavity, beyond a natural or artificial body orifice. Non-invasive techniques for the assessment of cerebral lateralization can be further subdivided into neuroimaging techniques and be-havioural techniques.

Neuroimaging techniques include both anatomical techniques, which create "constructed" images of brain structure, and functional techniques, which generate a series of dynamic brain images reflecting ongoing brain activity (Ganou, Kollias, Koidou, & Grouios, 2012). The anatomical techniques, which are the classical methods to image the brain, comprise computed tomography and structural magnetic resonance imaging. The functional techni-ques contain both direct (electroencephalography and magnetoencephalography) and indi-rect (positron-emissiontomography, single photon emission computed tomography and functional magnetic resonance imaging) measures of neural activity, which basically meas-ure haemodynamic responses or differences in metabolic concentrations to cognitive stimu-lation (for more information see Cohen & Sweet, 2011; Hüsing, Jäncke, & Tag, 2006).

Neuroimaging have offered a broad range of investigative tools to basic (e.g., Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni, 2006; Jansen, Menke, Sommer, Forster, Bruchmann et al., 2006; Tomasi & Volkow, 2012) and clinical (e.g., Desmond, Sum, Wagner, Demb, Shear et al., 1995; khondi-Asi, Jafari-Khouzani, Elisevich, & Soltanian-Zadeh, 2011; Oertel, Knöchel, Rotarska-Jagiela, Schönmeyer, Lindner et al., 2010) laterality research that fulfill the popular fantasy of being able to ''read the mind,'' albeit in the form of ''seeing the brain'' both struc-turally and functionally (Kerr & Denk, 2008).

Over the past 20 years, evidence for atypical cerebral lateralization in individuals with DS has been adduced using various neuroimaging techniques (Azari, Horwitz, Pettigrew, Gra-dy, Haxby, et al., 1994; Menghini, Costanzo, & Vicari, 2011; Pinter, Eliez, Schmitt, Capone, & Reiss, 2001). However, despite the large and growing literature describing patterns of brain structure and function in the healthy and diseased human brain, scientific research on Down syndrome has not been well integrated into the mainstream of human neuroimaging re-search. Nevertheless, a few investigators have demonstrated success in applying digital imaging technology in individuals with DS.

For example, Uecker, Mangan, Obrzut and Nadel (1993) argued that diffuse language later-alization in individuals with DS is likely to be a contributor to their poor visuospatial per-formance. Frangou, Aylward, Warren, Sharma, Barta et al. (1997) investigated whether the anatomic substrate for language are abnormal in DS. They examined volumetric Magnetic Resonance Imaging (MRI) measures of the superior temporal gyrus and the planum tempo-rale for community-dwelling individuals with DS and matched healthy comparison sub-jects. It was found that brain abnormalities in DS were not uniform. Specifically, the planum temporale volume of the individuals with DS was smaller than that of the healthy subjects. The volume of the superior temporal gyrus in the DS individuals was proportionally similar to that of the comparison group. For the subjects with DS, neither superior temporal gyrus nor planum temporale volume was significantly correlated with performance on language tests. Losin, Rivera, O'Hare, Sowell, and Pinter (2009) compared functional Magnetic Reso-

nance Imaging (fMRI) activation patterns during passive story listening in young adults with DS and approximately age-matched, typically developing controls. They found that individuals with DS exhibited differences in blood oxygen level dependant activation patterns compared to a typically developing group during the fMRI story-listening task. In particular, their results indicated that the DS group showed almost no difference in activation patterns between the language (forward speech) and non-language (backward speech) conditions. Menghini, Costanzo and Vicari (2011) investigated regional grey matter density in adolescents with DS compared to age-matched controls and correlated MRI data with neuropsychological measures in the DS group. Their findings revealed that a number of brain regions subserved the neuropsychological abilities of participants with DS. Although adolescents with DS showed typical organization of brain structures related to some cognitive abilities, in particular spatial memory and visuoperception, they presented abnormal brain organization related to other cognitive domains, such as linguistic and verbal memory. Jacola, Byars, Chalfonte-Evans, Schmithorst, Hickey et al. (2011) used fMRI to investigate neural activation during a semantic-classification/object-recognition task in individuals with DS and typically developing control participants. A comparison between groups suggested atypical patterns of brain activation for the individuals with DS.

Behavioural techniques that have frequently been used to assess cerebral lateralization include those that involve measurement of perceptual asymmetries, those that engage evaluation of sensory asymmetries and those that implicate determination of motor (or manual) asymmetries.

Studies of perceptual asymmetries have been utilized to explore lateral dominance of brain function and comprise dichotic, dichoptic and dichaptic stimulation. The rationale underlying the dichotic listening technique is that contralateral projections from each ear override ipsilateral projections when both ears are simultaneously presented with an auditory stimulus (e.g. a speech sound, digit or a musical tone) and the subject has to report what he/she has heard (Kimura 1967). Individuals with left hemisphere dominance for speech generally show a right-ear advantage for verbal stimuli. The stimuli, most commonly consonant vowel syllables or monosyllabic words, are presented to the participant via ear-phones. Right-handers commonly exhibit a right ear advantage for verbal stimuli (e.g., Elliot & Weeks, 1993; Hugdahl, 2005), although individual differences seem to affect performance (e.g., gender, age) (Cowell & Hugdahl 2000). Empirical research, using dichotic listening techniques, has stressed asymmetry at the perceptual level in individuals with DS (e.g., Bowler, Cufflin, & Kiernan, 1985; Bunn, Welsh, Simon, Howarth, & Elliott, 2003; Hartley, 1981).

In the dichoptic presentation technique (or divided visual field technique), the subject is asked to report verbal stimuli (letters, words) that are rapidly flashed tachistoscopically into one visual half-field, thereby, limiting visual input to the contralateral hemisphere (Banich, 2003). The very short tachistoscopic presentation time prevents possible eye movements and, thus, bilateral cortical projection of the stimuli. Speech stimuli presented in the right visual field and, thus, transmitted primarily to the left hemisphere are recognized and named more rapidly and certainly than stimuli presented in the left visual field (McKeever & Huling, 1970; Hines, 1972). The dominance of the left hemisphere is shown more distinct-

ly in recognition of abstract rather than concrete nouns (Ellis & Shepard, 1974, Hines, 1978) and also of words that only elicit a visual imagination with difficulty (Day, 1979). Right-handers usually show a right visual field advantage for verbal stimuli, as determined by the speed and correctness of the responses (Belin, Jullien, Perrier, & Larmande, 1990). A limited body of literature, using dichoptic presentation techniques, has documented the existence of perceptual asymmetries in individuals with DS (e.g., Chua, Weeks, & Elliott, 1996; Weeks, Chua, Elliot, Lyons, & Pollock, 1995).

The dichaptic stimulation technique requires the subject to feel two different objects with meaningless shapes presented one to each hidden hand at the same time (Witelson, 1974). Upon dichaptic examination, the subject is asked to identify the two shapes from among a collection of six visually displayed shapes (Springer & Deutsch, 1981). Thus, hemispheric differences in haptic perception might be uncovered because of the complexity of the task, by making verbal mediation impossible, or by interfering with the interhemispheric transfer of information through the activation of homologous cortical areas. It has been shown that when meaningless stimuli are used, perceptual asymmetries are usually found in favor of the left hand for right-handed individuals (Benton, Harvey, & Varney, 1973; Dodds, 1978; Verjat, 1988), which reflects a better treatment of spatial information by the right hemisphere. Experimental data, using dichaptic stimulation techniques, have supported the existence of perceptual asymmetries in individuals with DS (e.g., Chua, Weeks, & Elliott, 1996; Elliott, Pollock, Chua, & Weeks, 1995; Weeks, Chua, Elliot, Lyons, & Pollock, 1995).

Laterality researchers have increasingly come to recognize the importance of sensory asymmetries in determining observed patterns of cerebral dominance (Dittmar, 2002). Lateral asymmetries in the use of sensory organs, based on their preferential use or/and functional primacy in a specific situation, are among the most obvious functional lateral preferences (Hellige, 1993), and they figure prominently in explanations of our evolutionary past (Corballis, 1989), of ontogenetic development (Best, 1988; Levy, 1981), and of various abnormalities (Geschwind & Galaburda, 1985). The rationale for using the sensory asymmetries paradigm in the n the context of brain laterality is based on the presumption that difference in sensory performance between sensory stimuli presented to a sensory organ contralateral or ipsilateral to the dominant hemisphere would reflect a hemispheric bias in their attribution strategy (Porac, Coren, Steiger, & Duncan, 1980). Sensory asymmetries are most prominent with respect to the auditory (e.g., Reiss & Reiss, 1998), visual (e.g., Porac & Coren, 1976), tactile (e.g., Harada, Saito, Kashikura, Sato, Yonekura et al., 2004) and chemical senses [taste (e.g., Faurion, Cerf, Van De Moortele, Lobel, MacLeod et al., 1999) and smell (e.g., Royet & Plailly, 2004)]. As far as we know, no study to date has examined sensory asymmetries in DS individuals.

Motor indices of laterality, namely hand and foot preference and performance, have been used extensively to explore fundamental properties of the human brain, such as lateralization of brain functions, both in typically developing individuals (e.g., De Agostini & Dellatolas, 2001; Reiss, Tymnik, Kogler, Kogler, & Reiss 1999) and individuals with DS (e.g., Porac, Coren & Duncan, 1980; Grouios, Sakadami, Poderi & Aleuriadou, 1999). The most commonly used index of laterality is handedness. The main consideration in the assessment of hand-

edness is the use of different handedness measures, which produce different types of handedness. For example, hand preference can be assessed using questionnaires (e.g., Briggs & Nebes, 1972; Oldfield, 1971) on a five-scale continuum ranging from strong left-handers to strong right-handers. Alternatively, researchers have used preference measures to distinguish between left and right-handers (2 categories), excluding intermittent hand preferences (e.g., Coren & Porac, 1980), or right and non-right handers (2 categories) (e.g., Ypsilanti, 2009) or right-handers, left handers and ambiguous (or mixed) handers (3 categories) (e.g., Cornish & McManus, 1996).

In attempting to clarify both the conceptual and theoretical issues surrounding handedness assessment methodology, it is important to discriminate between "direction of hand preference", "degree of hand preference" and "consistency of hand preference" (Cornish & McManus, 1996). Direction of hand preference refers to the degree of dexterity or sinistrality that an individual exhibits (Bishop, 1990). Degree of hand preference is determined by whether an individual consistently exhibits a specific hand preference *across* several tasks or behaviours (Cornish & McManus, 1996). Consistency of hand preference is ascertained by whether an individual exhibits a specific hand preference for the same task on several occasions (Cornish & McManus, 1996). Consistency of hand preference was previously described by Palmer (1964), which he termed "variable hand preference" and postulated to be increased in left-handers. Moreover, the degree of hand preference was also previously described by Palmer (1964) which he termed "ambidexterity or mixed motor preference" referring to the degree of hand differentiation across different tasks.

Classification of handedness is further complicated by the fact that a researcher may assess hand preference (be that the direction, degree, or consistency) by a self-reported questionnaire (e.g., Briggs & Nebes, 1972) or a behavioural measure of hand preference (e.g., Bryden, Pryde, & Roy, 2000) or observation of hand preference (Porac & Coren, 1981) and/or hand performance or hand skill, which evaluates the proficiency of one hand over the other in performing a specific task (e.g., pegboard). The advantage of accessing hand preference is that one can evaluate several tasks (e.g., writing, throwing, cutting and dealing cards), rather than assessing hand performance on one task. However, assessing hand performance assists in the more qualitative understanding of handedness by allowing individuals to document their relative proficiency of one hand over the other. Most researchers (e.g., Porac & Coren, 1981; Bishop, 1990) agree that the assessments of hand preference and hand skill are two qualitatively different measures (i.e., they measure different things) of handedness. The mechanisms that mediate preference and performance are different representing two dimensions of laterality. In essence hand preference is mediated more by cognitive mechanisms that support the choice of hand-use, while hand skill may be less mediated by cognitive mechanisms and more supported by motoric systems. Annett, Hudson and Turner (1974) have supported the use of performance measures, suggesting that the relative proficiency of one hand over the other would most likely lead to increased preference of the more skilled hand.

The assessment of preference in populations with DS using questionnaires has been scarce since most clinical groups document ID, which may interfere with the process of answering

questionnaires (even if those are read to them). It has become very common during the pasts decades to use behavioural measures of hand preference (e.g., Bryden, Pryde, & Roy, 2000; Bishop, Ross, Daniel, & Bright, 1996) or observation of hand preference on a number of tasks (Porac & Coren, 1981). These tasks are comprised of 10-12 preference measures (to assess degree of hand preference), which are examined twice (to assess hand consistency) and handedness is usually evaluated on a three point scale of preference; left, right, mixed. However, studies have used the demonstration of hand preference based on the items of an inventory and a five-point scale has been used classifying individuals as strongly left, weak left, ambitexter, weak right, strongly right (Van Strein, Lagers, van Haselen, van Hagen, de Coo, Frens, & van der Geest, 2005). An alternative example of such a task is the WatHand Box Test (Bryden, Pryde, & Roy, 2000), which assesses direction and consistency of hand preference using a variety of unimanual tasks (e.g., lifting a cupboard door, using a toy hammer, placing rings on hooks and tossing a ball). In addition, Bishop's card reaching task (Bishop, Ross, Daniel, & Bright, 1996) that provides a measure of the degree and the direction of hand preference has commonly been used in individuals with neurodevelopmental disorders (see Desplanches, Deruelle, Stefanini, Ayoun, Volterra, Vicari et al, 2006).

Performance measures of handedness are used less often to assess the relative proficiency of on hand over the other in individuals with neurodevelopmental disorders. Tasks that have commonly been utilized to assess hand skill are finger tapping (Elliott, Edwards, Weeks, Lindley, & Carnahan, 1987; Elliott, Weeks, & Jones 1986) and the pegboard (e.g., Cornish & McManus, 1996; Cornish, Pigram, & Paw, 1997).

Other laterality indexes, such as ear, eye and foot, are also assessed both as preference and as performance. For example, foot preference can be assessed using a questionnaire or using a demonstration of foot preference across a number of tasks (e.g., Porac & Coren, 1981). Moreover, foot performance can also be examined by assessing the relative proficiency of one foot over the other. Up until now, no study that we know has specifically addressed relative foot performance in individuals with DS.

3. Atypical laterality in individuals with Down syndrome (Dichotic listening studies)

In dichotic listening studies the participants selectively attend one of the two messages presented simultaneously in both ears indicating a left or right ear advantage for linguistic material. Most evidence agrees that right-handed individuals with DS exhibit a unique pattern of ear dominance that is syndrome-specific and cannot be attributed to the mental retardation per se (Heath & Elliot, 1999). Support for this dissociation in ear preference comes from various studies assessing individual with DS, individuals with mental retardation (non-DS) and typically developing participants (e.g., Hartley, 1981; Pipe, 1983; Elliot & Weeks, 1993; Heath & Elliot, 1999; Giencke & Lewandowski, 1989). There is increased evidence for left ear/right hemisphere dominance for language in right-handed individuals with DS, which is indicative of a reversed cerebral specialization for speech perception (see Elliot, Weeks &

Chua, 1994 for a meta-analysis). This reversed pattern has been linked to the poor linguistic abilities of these individuals although dissociation between laterality for speech perception and speech production that involves oral motor systems has also been suggested (Elliot, Weeks, & Elliot, 1987; Giencke & Lewandowski, 1989; Heath & Elliot, 1999). During the past decade, studies explored the issue of the dissociation of lateralized systems for speech perception and speech production in individuals with DS using a verbal-motor task that tapped interhemispheric integration (Welsh, Elliot, & Simon, 2003). Their results supported their model of functional dissociation between perception and oral-motor production for speech stimuli that are typically supported by the same cerebral hemisphere in typically developing individuals. Moreover, this atypical pattern of cerebral specialization is specific to DS and is not observed in other populations with mental retardation (non-DS) of unknown etiology.

Unlike typically developing individuals, DS people exhibit right hemisphere lateralization for receptive language and a left hemisphere lateralization for the production of simple and complex movement. This separation of speech perception and motor movement in addition to the morphological callosal deficiencies (causing poor intrahemispheric communication) may be responsible for the verbal difficulties of DS individuals (Heath, Grierson, Binsted, & Elliott, 2007).

Pipe (1983) used dichotic listening tasks to assess language laterality in young children with DS, individuals with mental retardation (non-DS) and typically developing individuals. Their results indicated an atypical left-ear right-hemisphere advantage for speech stimuli in individuals with DS a pattern that was only observed in this clinical group. Non-DS individuals with mental retardation exhibited a right-ear left-hemisphere advantage for speech stimuli a pattern that was similar to typically developing individuals. In accordance with With Elliott, Edwards, Weeks, Lindley and Carnahan's (1987) study, Pipe (1983) observed the unique pattern of ear preference in individuals with DS, which seems to be expressed over and above the degree of mental retardation and may be described as syndrome-specific. It should be noted here that most researchers (e.g., Pipe, 1983; Elliott, Edwards, Weeks, Lindley, & Carnahan, 1987 Heath & Elliot, 1999) have linked this unique pattern of cerebral laterality for language in individuals with DS with the weak linguistic abilities that they exhibit. However, further research assessing different clinical syndromes that also exhibit linguistic deficits (e.g., Williams syndrome) using dichotic listening tasks is needed to support this hypothesis.

On the other hand, Paquette, Bourassa and Peretz (1996) documented a left ear advantage in individuals with ID of unknown etiology. Their results indicated a left ear/ right hemisphere advantage for speech stimuli in both impaired groups and the opposite pattern in typically developing individuals. This pattern of ear preference supports the notion of atypical cerebral laterality in individuals with mental retardation as a consequence of the early brain damage that affects intellectual functioning and cerebral specialization.

The importance of studies using non-invasive techniques, such as dichotic listening and handedness, to assess cerebral laterality in individuals with mental retardation is of vast importance. Firstly, non-invasive measures are easy and safe to administer to such populations and produce significant information to researchers in this field. Secondly, such

studies provide insight into the functioning of the brain and its lateralization. They also provide evidence for the representation of cognitive systems within the brain. For example, it may be suggested that the brains of individuals with DS may represent processing centers bilaterally causing a delay in the production of relevant cognitive and motor material. In addition, by combining neuroimaging with behavioral laterality techniques one can infer that certain brain areas are predominately involved in specific processes, while other areas are unable to execute their intended function. For instance, perhaps the weak collaboration of the two hemispheres is due to the thinner corpus callosum in individuals with DS (Wang, Doherti, Hesselink, & Bellugi, 1992) that may cause the isolation of the functions of the hemispheres enhancing weak intra-hemispheric integration at least for verbal-motor stimuli (Welsh, Elliot, & Simon, 2003).

4. Atypical laterality and Down syndrome (handedness studies)

Ear preference using dichotic listening tasks indicates a syndrome- specific pattern of cerebral laterality in individuals with DS. This pattern can perhaps be documented using other laterality indexes, such as hand, foot and eye preference. To date there has not been a study assessing individuals with DS on various laterality indexes using preference and performance measures and controlling for the effect of age, gender and degree of mental retardation. Such studies are currently been undertaken in our laboratory to assist further in the understanding of atypical laterality in individuals with DS.

However, handedness studies in individuals with DS have been reported since the 70's. Pickersgill and Pank (1970) assessed the prevalence of left handedness in individuals with DS, individuals with mental retardation non-DS and typically developing individuals. They found a higher prevalence of left-handedness in individuals with mental retardation non-DS compared to individuals with DS and typically developing adults. More specifically, the prevalence of left-handedness in typically developing individuals in their sample was 15.6% and that of individuals with DS 18.7%, while individuals with mental retardation non-DS exhibited an almost twofold increased prevalence of left-handedness (31%).

In a later study, Batheja and Mc Manus (1985) explored the prevalence of left-handedness in individuals with DS, individuals with mental retardation (non-DS) and typically developing Individuals, matched for age, and found no difference between the two clinical groups (DS=27% left-handers, non-DS= 29% left-handers), although there was a marked difference in the non-clinical groups (age matched controls=11% left-handers).

In a similar study, Pipe (1987) assessed hand preference in individuals with DS, individuals with mental retardation non-DS and age-matched controls including her families to determine whether familial sinistrality is documented in these populations. Their results indicated that the two clinical groups, regardless of their etiology (DS or non-DS) exhibited 35-36% of non-right handedness (i.e., left and mixed handedness) and increased familial sinistrality compared to the non-clinical population. The authors explained that the increased prevalence of mixed handedness and familial sinistrality in individuals with mental retardation

couldn't support Satz's (1973) model of pathological left-handedness. If non-right handedness is caused by early brain insult, as the model suggests, then there should not be an increased prevalence of familial sinistrality in these populations. Rather as Batheja and McManus (1985) suggested non-right handedness may be the result of any biological disturbance causing variability in cerebral asymmetry. Alternatively, specific hormones such as testosterone, delays the development of left-hemisphere functions resulting in increased prevalence of non-right handedness in clinical populations.

Lewin, Kohen and Mathew (1993) investigated handedness in individuals with DS, epilepsy and autism. Their results indicated a significantly increased prevalence of non-right handers in all three populations with no differences between the three groups and no differences associated with the level of mental retardation as reported elsewhere (e.g., Hicks & Barton, 1975). It was proposed that the theory of left-handedness (Satz, 1972) may explain the increased incidence of non-right handers in individuals with epilepsy in which focal brain damage may be assumed, however, it may not hold true for individuals with DS or autism. The theory of increased randomness (Palmer, 1964) may explain this pattern in individuals with learning disabilities, since the arrested development of the nervous system may lead to the undifferentiation of the two hemispheres documented by the increased prevalence of non-right handers in these populations. Table 1 below presents research using laterality indexes in DS and ID.

Findings from our laboratory confirm the existence of an atypical pattern of handedness preference in individuals with DS (n=50) and ID (n=50), compared to typically developing (TD) individuals (n=100) (Ypsilanti, 2009) (Figure 1). Specifically, our results demonstrate no significant differences between DS and ID individuals with similar level of intellectual functioning (mean IQ=43). However, they indicate statistically significant differences between both clinical groups and TD individuals (χ^2= 46.86, d.f.=2, p<0.01).

In reviewing studies of atypical laterality in individuals with DS, compared to individuals with ID (non-DS) and typically developing individuals, two conclusions can be drawn. Firstly, in the existing literature there seems to be inconsistent findings even when similar methodologies are employed. For example, Pickersgill and Pank (1970) found no significant differences in laterality in individuals with DS and typically developing individuals, while other studies have found such differences consistently (e.g., Batheja & McManus, 1985; Pipe, 1987). The reason for this discrepancy may be linked to various laterality measures that have been used to assess hand preference in individuals with neurodevelopmental disorders as well as the different age groups that have been selected in each case. Moreover, differences in the degree of mental retardation may have interfered with the results of different studies. Secondly, few studies have taken into account the fact that individuals with DS do not exhibit focal brain lesion during fetal development, which has converted them from natural right-handers to pathological left-handers as in the cases of individuals with focal brain injury in the left hemisphere (Satz, 1972). As Batheja and McManus (1985) proposed it is more likely that the difference in the prevalence of hand preference may be due to "… any form of biological noise" (pp. 66) (Batheja & McManus, 1985) that disrupts the development of typical asymmetry in these individuals at its genesis.

Study no.	Reference	Participants	N[1]	Preference/ performance	Indices	Results
1	Gordon (1921)	ID		Preference	Hand	LH 18% LH 7%
2	Merphy (1962)	ID, DS	64	Preference	Hand	LH 31% of ID LH 13% of DS
3	Lenneberg, Nickols and Rosenberger (1964)	DS	61	Preference	Hand	M 42.6%
4	Clausen (1966)	ID	276	Preference	Hand	LH 17%
5	Rengstroff (1967)	ID	395	Preference	Hand, eye	81.8% RH 18.2 LH - 48.5% RE 51.4 LE%
6	Peckersgill & Pank (1970)	ID, DS	32	Performance	Hand	LH 18% in Ds LH 31% in ID
7	Hicks & Barton (1975)	ID	550	Preference	Hand	LH 20.7% * Mild & Moderate: (13%) Severe & Profound: (28%)
8	Silva & Satz (1979)	ID	1409	Performance	Hand	LH 15.5 M 12.7%
9	Porac, Coren, & Duncan (1980)	ID	128	Preference	Hand, eye, ear, foot	LH 15.9 M 44.2%
10	Burns & Zeaman (1980)	ID	20	Preference	Hand, eye, ear, foot	Hand is more lateralized than foot, ear, eye in both groups.
11	Hartley (1981)	ID, DS		Performance	Ear	LEA in DS
12	McManus (1983)	ID	68	Preference (mother's report)	Hand	LH 13.2
13	Pipe (1983)	ID, DS		Performance	Ear	LEA in DS
14	Bradshaw, Hick & Kinsbourne (1984)	ID	232	Performance	Hand	More LH
15	Elliot, D (1985)	ID DS	38	Preference/ performance	Hand	
16	Batheja & McManus (1985)	ID, DS	130	Performance	Hand	LH 27% LH 29% LH 11%
17	Elliott, Weeks & Jones (1986).	DS		Performance	Hand	DS same asymmetry on finger-tapping

Study no.	Reference	Participants	N[1]	Preference/ performance	Indices	Results
18	Searleman, Cunningham & Goodwin (1987)	ID	90	Preference/ performance	Hand	LH 17.8 M 5.6
19	Soper et al., (1987)	ID	73	Preference	Hand	LH 9.6%, M 45.2%, RH 45.2%
20	Pipe (1987)	ID, DS	318	Preference	Hand	M 35%* LRH 36%* LRH 18%
21	Elliot et al. (1987)	DS	12	Preference/ performance	Hand	
22	Lucas et al., (1989)	ID	238	Preference	Hand	LH 17.4% mild LH 28.0% severe
23	Morris & Romski, (1993)	ID	50	Preference	Hand	LH 19%, LRH 32%, RH 49%
24	Paquatte et al (1996)	ID	16	Performance	Ear	LEA in ID
25	Mandal et al (1998)	ID	50	Preference	Hand	Mixed handedness.
26	Grouios et al. (1999)	ID	73	Preference	Hand	LH 17.8%, LRH 38.4%, RH 43.8% LH 9.6%, LRH 4.1%, RH 86.3%
27	Vlachos & Karapetsas, (1999)	DS	41	Preference	Hand	LH & LRH in DS
28	Heath & Elliot (1999)	DS	10	Performance	Ear	
29	Carlier et al., (2006)	DS, WS	79	Preference		
30	Leconte and Fagard (2006)	ID	30	Preference	Hand Eye Foot	Crossed Eye-hand
31	Desplanches et al, 2006			Preference		
32	Mulvey, Ringenbach & Jung, 2011	DS	25	Preference & perfromance	Hand	Reduced hand asymmetry in bimanual coordination
33	Carlier et al., 2011	DS, WS, DiGeorge syndrome		Preference	Hand Eye, Ear & Foot	Increased mixed handedness and footedness in all groups, related to degree of ID.

1Sorted by year of study

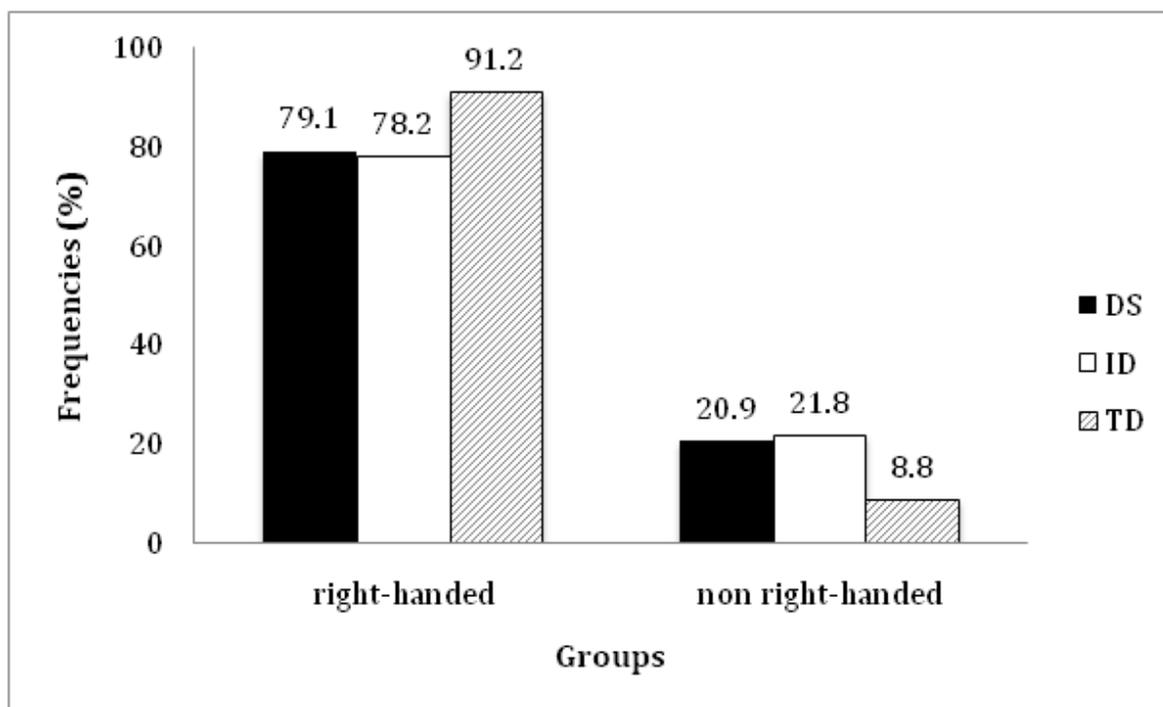**Table 1.** Laterality indices in ID and DS.

Figure 1. Frequencies of right and non-right handed individuals with DS, ID and TD.

5. Theoretical explanations of atypical laterality

Several accounts have been put forward to explain the increased incidence of atypical laterality in individuals with ID. It has been suggested that theories on atypical laterality fall into two categories; namely, pathological and natural (Satz, 1973). However, for the purposes of clarity this discrimination will not be adapted in the present paper. Rather a detailed analysis of all the theories will be presented including those that are scarcely discussed in the literature.

One of the most prominent theories has been put forward by Geschwind and Galaburda (1987), who implicated the levels of testosterone in the development of atypical laterality. According to the theory, several genetic factors, such as chromosomes and antigens, as well as environmental factors that affect fetal development, like the endocrine environment and the cyclic variation, alter the levels of testosterone to the fetus. This effect is directly linked to both the delayed growth of the left hemisphere and the increased growth of the right hemisphere particularly in the posterior regions. The decreased growth of the left hemisphere has been linked to mental retardation and poor verbal ability, which are some of the characteristics of individuals with neurodevelopmental disorders. In essence, the model predicts that the increased levels of testosterone will have an impact on the development of the left hemisphere, causing reduced language and visual-spatial dominance. Therefore, individuals with this condition will exhibit increased left and mixed handedness compared to the normal population. In support of their theory, Geschiwind and Galaburda (1985a, 1985b,

1985c) presented a series of studies associating atypical laterality (or "anomalous domi-nance") with developmental learning disorders, autism and immune disorders.

Although Geschwind's and Galaburda's (1987) theory has been considered one of the most prominent theories in the field of cognitive neuropsychology, it has been strongly criticized for its complexity and its arbitrary predictions (e.g., McManus & Bryden, 1991; McManus, Bryden, & Bulman-Fleming, 1994; Annett, 1994; Previc, 1994). Bryden McManus and Bul-man-Fleming (1994) suggest that the relationship between language dominance and hand-edness, as discussed by Geschwind and Galaburda (1987), is weak and the conclusions drawn based on this assumption are poorly supported by empirical findings. Moreover, the predictions made by Geshwind and Galaburda (1987) are farfetched and the experimental data cannot support the numerous associations that are predicted by theory. On the other hand, the theory, although long and complex, contributed greatly to the understanding of the biological factors (i.e., hormones) that may be linked to atypical laterality and triggered a large number of studies in atypical laterality and neurodevelopmental disorders.

Genetic theories have also been put forward to explain atypical laterality (Annett & Alexander, 1996; Bryden & McManus, 1985). The main focus of these genetic theories was to explain the origin of left and right-handedness in normal populations (Annett 1972, 1985). More specifically, Annett's (1972) theory, referred to as "right-shift theory", explained the exhibition of right and left handedness as the outcome of left hemisphere speech induced by a single gene. In the case of atypical handedness Annett (1994) suggested that atypical de-velopmental effects could trigger randomness in the absence of the right-shift gene and in-hibit the "natural" cerebral asymmetry that is observed in typical development. Moreover, individuals lacking the gene for right hemisphere speech (rs+ gene) are at risk for various difficulties that affect language expression and phonology such as dyslexia. In other words, Annett (1985) proposed that atypical laterality may be a "... natural variation in cerebral asymmetry" (pp. 241) triggered by the absence of the right-shift gene (Annett, 1994).

Previc (1991) postulated that cerebral asymmetry derives from the asymmetric development of the vestibular system (left ear dominance in approximately 70% of the population), which is established during prenatal life and is directly linked to the postural position of the fetus and the pattern of maternal movements during the final trimester of the pregnancy. More-over, the anatomy of the female uterus induces fetuses in the final trimester of pregnancy to be positioned "… with their head to the left side of the mother's midline and their right ear facing outward" (pp. 301) (Previc, 1991). This postural asymmetry of the fetus and the moth-er favours a sinistral vestibular dominance at birth, which is documented by the dextral lie preference of newborns and is correlated with the development of right hand preference lat-er in life. The asymmetrical development of the two vestibular organs, the ear and the laby-rinth, may be responsible for the asymmetry of the left and right hemisphere and the difference in ear preference documented in the literature using dichotic listening tasks (e.g., Heath & Elliott, 1999). Previc (1991) proposed a link between poor motoric lateralization (i.e., mixed or left handedness), the vestibular system and neurodevelopmental disorders that are associated with vestibular dysfunction; namely autism, dyslexia and deafness. In es-sence, Previc's (1991) theory predicted increased percentages of non-right handedness in

these disorders, in addition to other neurodevelopmental disorders, that exhibit abnormalities in the brain stem, the basal ganglia, the cerebellum and the temporal lobes, since these systems are directly affected or affect the vestibular system. Also, increased percentages of poor motoric dominance (i.e., non-right handedness) are likely to exist in pre-term infants, since they have not been exposed long enough to the right face position allowing for right handedness to be established. Previc's (1991) theory initiated a new era in the research of human laterality. The presence of prenatal factors that affect and essentially define motoric dominance in humans in combination with genetic, environmental and cultural theories could provide an important framework for the development of a stronger and more inclusive theory that encompasses strengths of all other theories.

An alternative model attempting to explain the increased incidence of atypical laterality in individuals with neurodevelopmental disorders is the theory of pathological left-handedness (Satz, 1973) According to this account, there is a subgroup of left-handed individuals which are described as pathological left handers. This subgroup was genetically natural right-handers, but suffered early brain insult to the left hemisphere causing a mild dysfunction of the contralateral hand for motor movements. The result of this dysfunction was a switch of hand dominance to the other hand (i.e., left hand) to perform complex motor tasks. Therefore, although these individuals were genetically programmed to become right-handers having left hemisphere dominance for language an early brain insult (before the age of six) caused a switch hand preference making them pathological left-handers. This subgroup is differentiated for natural left-handers who have no history of brain insult early in development and are naturally born with left hand dominance. In addition, the model describes a subgroup of pathological right-handers who were natural left-handers but an early brain injury in the right hemisphere caused them to switch hand preference to the opposite hand, thus becoming pathological right-handers. The account of pathological left-handedness can predict the increased incidence of left-handers in populations with ID and epilepsy, since both groups seem to have brain abnormalities exhibited early in development. Therefore, within a population of individuals with mental retardation, there will be an 8% of natural left-handers, as in the typical population, and approximately another 8-9% who are pathological left-handers. This model would explain the almost twofold percentage of manifest left-handers in individual with mental retardation.

Several studies have provided evidence for the model of pathological left-handedness, since the initial account was put forward (Satz, 1973). However, the theory has been tested in cross cultural studies (Satz, Baymure, & Van der Vlugt, 1979), in studies using EEG recordings (Silva & Satz, 1979), in studies with individuals with left or right congenital hemiplegia (Carlsson, Hugdahl, Uvenbrant, Wiklund, & Von Wentd, 1992), in relation to familial sinistrality (Orsini, Satz, Soper, & Light, 1985; Pipe 1987) and degree of ID (Bradshaw-McAnulty, Hicks, & Kinsbourne, 1984) and has been termed the pathological left handedness syndrome (Satz, Orsini, Saslow, & Henry, 1985). Since the original study (Satz, 1973) Soper and Satz (1984) incorporated one more type of pathological handedness in their model, termed ambiguous handedness, to explain the increased incidence of mixed handedness in individuals with early brain insult. The new explanatory

model predicted increased incidence of ambiguous handedness in the more severe groups with neurodevelopmental disorders, such as infantile autism and severe ID (Soper & Satz, 1984), which has also been reported elsewhere (e.g., Tsai, 1982).

Although the above-mentioned theories contribute to the understanding of the increased incidence of non-right handers in individuals with neurodevelopmental disorders, the evidence for this link is far from conclusive. Satz's (1973) theory of pathological left handedness could account for the increased incidence of left handers in individual with focal brain injury, but in clinical populations with defuse brain damage (e.g., DS, Williams syndrome) and lack of hand preference (i.e., increased mixed handedness) the theory seems inadequate. Particularly in individuals with ID, it has long been recognized that ambiguous handedness rather than left-handedness is most commonly observed (e.g., Porac, Coren, Steiger, & Duncan, 1980). This lack of handedness would be documented by random hand preference in preference measures.

Palmer (1964) termed this observation "increased randomness" referring to the increased ambiguous hand preference in individuals with mental retardation. In particular, he postulated that handedness is a developmental process and could be utilized as an index of typical motor development. This developmental process progresses from a bilateral undifferentiated state early in infancy to a unilateral state that is viewed as a "… differentiation from a whole" (pp. 258) (Palmer, 1964), since it initiates from the trunks before the shoulders and then the hands. Therefore, Palmer (1964) proposed a maturational process that is linked to typical cerebral laterality and one-sidedness. If this maturational process is arrested or lagged it could cause increased randomness, which would be documented by lack of hand preference (i.e., ambiguous handedness). One of the main conclusions that could be drawn from Palmer's (1964) theory is that mixed and left-handedness has long been considered differentiated states and should be studied separately. Particularly in populations with neurodevelopmental disorders, "lack of hand preference" (i.e., mixed handedness) may be a more significant indicator of atypical cerebral laterality than left-handedness.

Along this vein, Bishop (1983, 1990) postulated that non right-handedness is an indicator of an immature development of the motor system, caused by diffuse brain abnormalities in individuals with mental retardation. In contrast to Satz's (1973) theory and other genetic theories, Bishop (1990) suggests that differentiated hand preference indicates mature motor development. According to Bishop (1990), studies assessing hand preference in individuals with mental retardation should utilize a control group matched for motor development rather than chronological or mental age. The question remains whether there is correspondence between motor and mental age and whether measuring motor age when assessing handedness can further contribute to the existing literature. To our knowledge, there are no published data on of handedness in neurodevelopmental disorders that utilises a control group matched for motor age. On the other hand, mental age as assessed using the WISC III (Wechsler, 1992) may also be problematic because the verbal subtests of the WISC III (Wechsler, 1992) may undermine the motor development of an individual with mental retardation. The link between mental retardation and motor retardation has not been widely investigated. Perhaps using the performance subscales of the WISC III (Wechsler, 1992), or

another measure of non-verbal intelligence (e.g., Raven, 1985), would be more appropriate for matching control groups. Further, research in the area of motor development and the assessment of handedness in relation to motor age are needed to clarify the issue.

A link has also been postulated between literacy and handedness, suggesting that cerebral organization may change as a result of schooling and literacy, although the evidence for this link is contradictory (Tzavaras, Kaprinis, & Gatzouas, 1981). In controversy with genetic theories, this approach suggests that literacy reinforces the left hemisphere dominance for language. According to the theory, there should be an increased number of individuals with atypical laterality among illiterate populations exhibiting right or bilateral dominance for language. Tzavaras, Kaprinis and Gatzouas (1981) examined this possibility using the dichotic listening technique as a measure of language dominance in an illiterate population and found an increased left-right ear difference in the illiterate population compared to the literate individuals. The authors suggested that this difference might be due to the poor strategic techniques used by illiterate subjects, which do not enhance bi-hemispheric participation for speech as in the educated brain. However, it has been found that aphasia is less severe and more provisional in illiterate patients suggesting a right hemisphere involvement of language in these individuals (Lecours, Mehler, Parente, Behrami, Tolipan, Cary, et al, 1988; Cameron, Currier, & Haerer, 1971). Castro-Caldas, Reis and Geurreiro (1997) in a review on literacy and laterality concluded that the empirical findings of studies from aphasic patients and dichotic listening tasks are inconclusive about the link between atypical laterality and literacy and further research is need to clarify this postulation. To the authors' knowledge, no studies have been reported linking the observed atypical laterality of individuals with neurodevelopmental disorders with literacy and schooling. However, a number of researchers propose that lateral preferences may be affected by the type of task used and may be related to the level of experience and practice that a group of individuals have (e.g., Bishop, 1983). If one accepts this notion, it is probable that individuals with mental retardation are less skilled than typically developing individuals with objects like pencils, scissors and playing cards, which are commonly used to assess hand preference in these populations. In this case, inconsistent hand preference when manipulating such objects may be affected by the immature behaviour exhibited by these individuals due to decreased experience. More specifically, the effect of limited schooling and skilfulness in individuals with mental retardation may have an indirect impact on lateral preferences particularly when the preference measures presented are school-related utilities.

Another line of research suggests that individuals with DS exhibit atypical neural activation in left/right hemisphere regions compared to typically developing individuals (Jacola, Byars, Chalfonte-Evans, Schmithorst, Hickey, Patterson, et al., 2011). In an fMRI study with 13 DS individuals, there was a positive association between visual-spatial ability and occipito-parietal and dorso-frontal activation exclusively in individuals with DS compared to control counterparts.

6. Epilogue

Research in laterality in individuals with DS has been fruitful. Findings from dichotic listening studies suggest that individuals with DS exhibit a unique pattern of lateralization of language, which is syndrome specific. Specifically, it has been repeatedly supported that there is a left-ear, right-hemisphere advantage for speech stimuli, unlike that observed in typical populations or individuals with ID of other aetiologies. Moreover, handedness studies demonstrate that lateralization of language may be pathological with increased incidence of left-handedness, left- footedness, left-eyedness and cross eye-hand preferences. Several theories have been put forward to explain this atypicality, including, hormonal, structural and neural anomalies related to the syndrome. This atypical pattern of functional lateralization, most likely contributes to the linguistic difficulties observed in individuals with DS, which are rather permanent. At the same time, limited educational and motor training leaves little space for improvement in linguistic and motor efficiency in individuals with DS. Other developmental milestones that are fundamentally delayed in individuals with DS obstruct the developmental transition from an undifferentiated state to a lateralized state.

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